

NATIONAL BUREAU OF STANDARDS REPORT

10 442

Progress Report
on
STABILIZING COMONOMER
I. SYNTHESIS AND CONFIRMATION OF STRUCTURE



U.S. DEPARTMENT OF COMMERCE
NATIONAL BUREAU OF STANDARDS

NATIONAL BUREAU OF STANDARDS

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Progress Report

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A STABILIZING COMONOMER:

I. SYNTHESIS AND CONFIRMATION OF STRUCTURE

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This investigation was supported in part by research grant DE02494-05 to the American Dental Association from the National Institute of Dental Research and is part of the dental research program conducted by the National Bureau of Standards in cooperation with the American Dental Association; the Dental Research Division of the United States Army Medical Research and Development Command; the Dental Sciences Division of the School of Aerospace Medicine, USAF; the National Institute of Dental Research; and the Veterans Administration.

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A STABILIZING COMONOMER: I. SYNTHESIS
AND CONFIRMATION OF STRUCTURE

Synopsis

A compound (BHM) was synthesized that can stabilize monomers by inhibiting premature polymerization but which can serve as a monomer in the polymerization after the initiator system is activated. The structural formula of BHM (3,5-di-tert-butyl-4-hydroxybenzyl methacrylate) was confirmed by NMR analysis.

A STABILIZING COMONOMER: I. SYNTHESIS
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There has been continued interest in improving the quality and tissue compatibility of dental composites and other biomaterials. One approach to these goals is the utilization of formulation ingredients that become an integral part of the polymeric network of such acrylic materials. Methacrylate monomers require the addition of stabilizers. These are polymerization-inhibiting compounds which prevent premature gelling during storage and give the user sufficient working time between mixing and hardening, to manipulate the material. Hydroquinone was used in early methacrylate resins¹ and composites.² Less discoloration occurred with the use of the monomethyl ether of hydroquinone, and even less with an antioxidant stabilizer BHT (butylated hydroxytoluene; 2,6-di-t-butyl-4-methylphenol).³

Continued efforts have been made to combine, in the same molecule, a sterically hindered phenol moiety (c.f., BHT³) and a copolymerizable group.^{4,5} If the latter group were a

methacrylate ester moiety, it could copolymerize with other reactive monomers in a formulation and thus become fixed and localized within the polymeric chains. This report describes the synthesis of one such compound. Part II will report stabilization and polymerization characteristics.

Materials and Methods*

Most of the materials used are listed in Table 1. They were used as received. The methacryloyl chloride (as supplied) contained 1% N,N-dimethylaniline as its stabilizer.

PREPARATION OF BHM .—The synthesis was carried out in a three-neck, round bottom flask, equipped with stirrer, thermometer, and dropping funnel. Pyridine (76 gm; 0.96 mole) and 4-hydroxymethyl-2,6-di-*t*-butylphenol, which also has been referred to as 3,5-di-*t*-butyl-4-hydroxybenzyl alcohol,^{4,6} (203 gm; 0.86 mole) were placed in the flask with stirring. To this slurry, just enough acetone (131 gm) was

* Certain commercial materials and equipment are identified in this paper to specify the experimental procedure. In no instance does such identification imply recommendation or endorsement by the National Bureau of Standards or that the material or equipment identified is necessarily the best available for the purpose.

added to give a clear solution. Methacryloyl chloride (99 gm; 0.95 mole) was then added dropwise over a period of three hours during which time the temperature varied between 24 and 41°C due to the exothermic reaction. As the reaction proceeded, a precipitate of pyridinium chloride was formed. Within 3 additional hours, the stirred suspension had returned to room temperature; it was then washed onto a vacuum filter with 37 gm of additional acetone. The clear, amber filtrate was cooled overnight in a covered Dewar vessel containing dry ice (solid carbon dioxide). The resulting precipitate was separated by vacuum filtration yielding 80 gm (31% theoretical yield, based on the phenol) of crystalline material containing a canary-yellow impurity. In like manner, serial recrystallizations from warmed methanol, heptane, hexane and pentane gave 23 gm of colorless crystals of BHM.

The large, transparent crystals had a melting range (corrected) of 58-59°C. The elemental analysis found, C 74.9; H 9.5 was in agreement with that calculated, C 75.0; H 9.3%, for BHM.

NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPIC ANALYSIS.—

The proton magnetic resonance spectrum of the compound as a 15 percent (w/v) solution in deuterated chloroform [CDCl_3 , containing 1 percent (v/v) tetramethylsilane] was obtained using

a Varian A-60 spectrometer run at 60 MHz. No attempt was made to control the temperature of the sample which was assumed to be at ambient conditions ($21 \pm 1^\circ\text{C}$).

Electronic integration of the spectrum to obtain the intensities of the various peaks was performed six times. The heights of the steps of the integration line were measured with a metric rule.

Results

The structural formula (Figure 1) was confirmed by nuclear magnetic resonance analysis. The frequency of absorption of each of the various protons relative to that for the protons in tetramethylsilane was measured on the δ scale⁷⁻¹⁰; this relative frequency is known as the chemical shift. The chemical shift values and proton assignments, based on cataloged NMR data⁷ and empirical rules^{8, 9} are given in Table 2.

Under proper operating conditions, the area under an absorption band, i.e. the intensity, obtained by integrating the spectrum, is proportional to the number of protons responsible for the absorption.¹¹ Based on this assumption, the measured intensities were converted to relative intensities by: (1) setting up the following system of simultaneous equations $\sqrt{w_i} \bar{I}_i = \sqrt{w_i} k N_i$ where w_i is a statistical weighting factor^{12, 13} inversely proportional to the variance of the intensity of peak "i", \bar{I}_i is the mean (average) measured intensity of peak "i", k is the proportionality constant relating the intensity of a peak to the number of protons responsible for the peak, and N_i is the number of protons responsible for peak "i"; (2) solving for k according to the principle of least squares^{12, 13}; and (3) dividing the measured intensities by the calculated value of k (assumed to be constant). In other words, $\bar{I}_i/k = I_{\text{experimental}}$, where $I_{\text{experimental}}$ is the found relative intensity.

The value for the found and predicted relative intensities are given in Table 2. Because of the way in which the relative intensity is defined, the predicted relative intensity is merely the number of protons of a given con-

figuration in the molecular formula.

For statistical purposes, the value of the standard error of the mean of the relative intensity for each peak is given in Table 2. This is defined as $s_i/\sqrt{n_i}k$, where s_i is the standard deviation of the measured intensity, n_i is the number of measurements of each intensity (six in this case), and k is a proportionality constant defined previously.

A cursory examination of the measured intensities revealed that the mean intensity for the t-butyl peak was approximately half the expected value. This discrepancy was ascribed to "saturation" effects caused by the overly-high intensity of the radiofrequency signal needed for observing the low intensity peaks.¹⁴ Since the error in the intensity of this peak was systematic (i.e. non-random),¹⁵ this mean intensity value was not considered in the above determination of k .

Statistical analysis¹² of the mean measured intensity values revealed that the error from regression (assuming the model shown, a linear equation with zero intercept) is

considerably greater than the error due to replication at the 95% confidence level. This does not necessarily show the compound to be impure since the assumption that the intensities of absorption bands are proportional to only the numbers of protons responsible for the absorption is only approximately correct.¹⁴

The same sample was analyzed using a lower-intensity radiofrequency signal and only the strong peaks ascribed to the t-butyl and methacrylate protons were integrated. The measured intensity values were converted to relative intensity values as before and are shown in Table 2 (2nd analysis).

The reproducibility of the chemical shifts is indicated by a comparison of the two analyses showing that the chemical shift values are in error probably by one or two units in the second decimal place.

That the methacryloyl chloride reacted with the benzylic hydroxyl group instead of with the sterically-hindered phenolic group, was evidenced by the chemical shift of the hydroxyl

proton in BHM (δ = 5.23 ppm) corresponding more closely with that found for BHT (δ = 4.97 ppm) than with the proton of the benzylic hydroxyl group (δ = 1.78 ppm) of the starting material (4-hydroxymethyl-2,6-di-t-butylphenol).

Discussion

A monomer that is also a polymerization inhibitor appears at first glance to be a paradoxical notion. However, there may well be applications for such a compound since it affords certain desirable features. For example, this compound would be expected to have advantages both with respect to polymerization kinetics and also from a toxicological viewpoint, although these features have not as yet been demonstrated.

With respect to hardening characteristics, the stabilizing comonomer would be free to diffuse to peroxy radical sites (or other oxygen radicals), engage in hydrogen transfer, and thus become a (relatively) stable free radical, unable to initiate monomer polymerization.¹⁶ This would give storage stability (shelf life) to the formulation. When a polymerization-initiator system is added, the mobile compound could, for a while inhibit or retard gelation and provide the necessary working time for manipulation of the composite or other

resin-based material. However, as polymerization proceeded (overriding the effects of the small concentration of this stabilizing comonomer), the methacrylate moiety would increasingly become involved in copolymerization. This would localize the molecule so that it could no longer diffuse to peroxy radical sites thus tending to increase the kinetic chain length or rate of hardening reaction. This "self-depleting" characteristic would tend to give the "snap-hardening" (abrupt polymerization and rapid development of ultimate physical properties) effect desired by dental practitioners.

From a toxicological point of view, the binding into the polymeric chains of the inhibitor's reaction products or of residual stabilizer, by copolymerization, would probably be desirable.¹⁷

There may be other advantages also, in regard to long-term resistance to autoxidation⁵ and improved adhesion by decreasing a source of weak boundary-layer materials due to the exudation of an otherwise unbound and relatively low-molecular-weight material.¹⁸

The synthesis of this compound further implements the more general scheme to provide the required formulation ingredients with optimum functionality, by utilizing maximum feasible molecular weights ("bulkiness") and by the ability to copolymerize so as to minimize undesired tissue penetration and untoward side effects.¹⁹ This copolymerizable stabilizer, BHM, constitutes an important member to be added to the growing list of such specialized biomedical materials.

Conclusions

Sterically hindered phenols are used as antioxidants and stabilizers for monomers that polymerize by way of free radicals. A compound, BHM, was synthesized that contained, in the same molecule a methacrylate moiety capable of polymerization in a methacrylate monomer system, and also a sterically hindered phenol group that is an effective stabilizer. This unusual combination is expected to have advantages both with respect to polymerization kinetics and also from a toxicological viewpoint since the compound or its reaction products would become part of the polymeric network.

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TABLE 2

NMR CHEMICAL SHIFTS, THE RELATIVE INTENSITIES
FOUND AND THOSE PREDICTED FOR BHM

δ (ppm)*	Proton Assignment	<u>First analysis</u>		S.E.†	$I_{predicted}$
		I_{found}^{\dagger}	§		
1.46	<u>t</u> -butyl		§	--	18
1.96	methacrylate methyl	3.2		0.04	3
5.09	benzylic	1.9		0.02	2
5.23	hydroxyl	1.0		0.02	1
5.54	vinylic	1.0		0.05	1
6.12	vinylic	0.9		0.04	1
7.18	aromatic	2.2		0.04	2
<u>Second analysis</u>					
1.46	<u>t</u> -butyl	18.0		0.17	18
1.98	methacrylate methyl	3.0		0.07	3

* The chemical shift of a proton⁷⁻¹⁰

† Mean relative intensity (defined in the text), the result of six integrations

‡ Standard error of the mean for the found relative intensity

§ Because of bias¹⁵ caused by saturation effects,¹⁴ the relative intensity value for the t-butyl group was not determined in the first analysis.

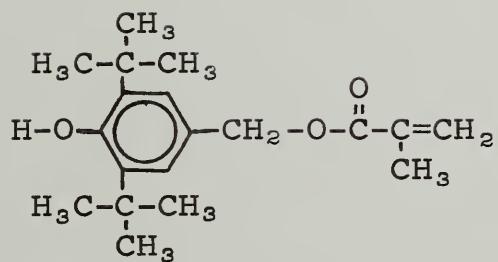


Fig. 1.—Structural formula of BHM
(3,5-di-tert-butyl-4-hydroxy-
benzyl methacrylate).

An alternative name for this compound is 4-methacryloxymethyl-2,6-di-t-butylphenol.

